Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 59, No. 22, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.01.020

Effects on Outcomes of Heart Rate Reduction by Ivabradine in Patients With Congestive Heart Failure: Is There an Influence of Beta-Blocker Dose?

Findings From the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) Study

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Objectives This study used the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) database to assess the impact of background beta-blocker dose on response to ivabradine.

Background In systolic heart failure, reduction in relatively high heart rates improves clinical outcomes when achieved with beta-blockers and even more so when the sinus node inhibitor ivabradine also is added.

Methods Among patients with systolic heart failure, sinus rhythm, and heart rate ≥70 beats/min on recommended background therapy, maximally tolerated beta-blocker doses were subgrouped as no beta-blocker, <25%, 25% to <50%, 50% to <100%, and 100% of European Society of Cardiology–suggested target doses. The impact of ivabradine on cardiovascular death or heart failure hospitalization (primary endpoint) was analyzed in each subgroup as time-to-first event using Cox models adjusted for heart rate. The statistical models assessed heterogeneity and trend of the treatment effect across subgroups, and an additional analysis was made adjusting for the interaction of randomized treatment with baseline heart rate.

Results The primary endpoint and heart failure hospitalizations were significantly reduced by ivabradine in all subgroups with <50% of target beta-blocker dose, including no beta-blocker ($p = 0.012$). Despite an apparent trend to reduction in treatment-effect magnitude with increasing beta-blocker dose, no variation in treatment effect was seen in general heterogeneity interaction tests ($p = 0.35$). Across beta-blocker subgroups, treatment effect was borderline nonsignificant only for the primary endpoint ($p = 0.056$), and significance was further lost after adjusting for interaction between baseline heart rate and ivabradine effect ($p = 0.14$).

Conclusions The magnitude of heart rate reduction by beta-blocker plus ivabradine, rather than background beta-blocker dose, primarily determines subsequent effect on outcomes. (Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study; ISRCTN70429960) (J Am Coll Cardiol 2012;59:1938–45) © 2012 by the American College of Cardiology Foundation

During the last 20 years, the treatment of symptomatic heart failure with systolic dysfunction has improved markedly, and the risk of death or morbidity has been dramatically reduced (1,2). The improvement has mainly been associated with the develop-

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Manuscript received November 21, 2011; revised manuscript received December 30, 2011, accepted January 3, 2012.

ment of pharmacological therapies. These now include a combination of neurohormonal antagonists with focus on modulation of the renin-angiotensin-aldosterone system and the sympathetic nervous system (3). Among those agents, beta-receptor antagonists have emerged as being particularly important.

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The mechanism for the effects of beta-blockers is unclear, but an association between the improvement of mortality and the degree of drug-induced heart rate reduction has been reported (4). Heart rate is a risk marker in the general population (5), as well as in those with coronary artery disease (6). In patients with systolic heart failure and in sinus rhythm included in the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) study, heart rate has been identified as a modifiable risk factor (7). Heart rate ≥70 beats/min in patients treated with a beta-blocker, as well as in those without a beta-blocker because of lack of tolerability of the drug, was found to be strongly related to the risk of worsening of heart failure or death due to heart failure. In SHIFT, reduction of heart rate by ivabradine, administered in addition to beta-blockers when heart rate exceeded 70 beats/min on beta-blockers alone, reduced subsequent adverse outcomes (8). There was no interaction in the effect of ivabradine between patients not taking a beta-blocker versus those treated (8). A remaining clinical question is whether beta-blocker dose at randomization impacts the response to ivabradine. The present analysis was initiated to explore this question using the SHIFT database.

Methods

Design and treatment. SHIFT was a randomized, double-blind, placebo-controlled, parallel-group clinical trial in patients with moderate-to-severe heart failure and left ventricular systolic dysfunction, undertaken in 677 centers in 37 countries. The study design has been reported elsewhere (9). In brief, patients included in the trial were men or women 18 years and older with stable symptomatic chronic heart failure of 4 or more weeks' duration with left ventricular ejection fraction ≤35%, who had been admitted to hospital for worsening heart failure within the previous 12 months, and who were in sinus rhythm and with a resting heart rate of ≥70 beats/min (measured by 12-lead electrocardiogram on 2 consecutive visits). Patients were randomized to receive treatment with ivabradine or placebo. The starting dose of study drug was 5 mg twice daily. After a 14-day titration period, the dose was increased to 7.5 mg twice daily, unless the resting heart rate was 60 beats/min or lower. The dose was adjusted throughout the study to 7.5, 5, or 2.5 mg twice daily according to resting heart rate and tolerability. At randomization and throughout the study, participants were expected to be on evidence-based medication for heart failure at guidelines-suggested doses if tolerated. When a participant was not on a beta-blocker or was not on the guidelines-suggested target dose, the investigator was required to provide a specific reason in a dedicated case-report form.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

CI = confidence interval

COPD = chronic obstruction pulmonary disease

ESC = European Society of Cardiology

The aim of the current analysis was: to compare characteristics of participants by baseline beta-blocker status; to assess reasons for not taking a beta-blocker or for not taking the target dose; to identify the baseline factors independently predicting those not taking a beta-blocker or, among those on a beta-blocker, not taking at least 50% of the target dose; and to investigate the effect of ivabradine treatment on study outcomes across the range of beta-blockers and doses. To this end, we categorized participants as taking or not taking a beta-blocker at randomization and subdivided those taking a beta-blocker into categories defined by the percentage of the target dose they were taking. These categories were defined as <25%, 25% to <50%, 50% to <100%, and 100% of the target dose as defined by the European Society of Cardiology (ESC) guidelines (10). A total of 107 of the 6,505 randomized participants were taking a beta-blocker that was not recommended in the guidelines and hence could not be categorized. These 107 participants were excluded from all analyses reported in this paper, leaving a total of 6,398 for analysis.

All study endpoints were adjudicated by an independent endpoint validation committee.

The study was approved by the ethics committee or institutional review board of every site, and each study participant had provided formal informed consent.

Statistical methods. Baseline characteristics of the patients at randomization were summarized as count (%) for categorical variables and mean ± SD for continuous variables. The distributions of these variables across the beta-blocker categories were compared by chi-square tests and analysis of variance for categorical and continuous variables, respectively, initially using tests of general heterogeneity and then using trend tests. The distribution of reasons given for a participant not to be taking a beta-blocker or, if taking a beta-blocker, not taking the target dose, were tabulated by beta-blocker category. The baseline factors independently associated with not taking a beta-blocker versus taking a beta-blocker were analyzed by fitting a multivariable stepwise logistic regression model to those factors significantly associated with not taking a beta-blocker in univariate analysis ($p < 0.05$). Results are given as odds ratios, 95% confidence intervals, and p values calculated from the Wald statistic. A similar analysis was conducted in those taking a beta-blocker to identify the factors associated with taking at least half of the target dose.

The effect of ivabradine treatment on heart rate reduction was studied in the 25 subgroups defined by baseline beta-blocker categories and heart rate categories (as previously

reported [7], by equally sized quintiles: <72 beats/min, 72 to <75 beats/min, 75 to <80 beats/min, 80 to <87 beats/min, ≥87 beats/min). The mean differences between the heart rate changes from baseline to 28 days for the placebo group and the ivabradine group were calculated and evaluated using 3-way analysis of variance (with treatment group, beta-blocker category, and baseline heart rate category as factors).

The impact of ivabradine treatment versus placebo on the primary study outcome of cardiovascular death or hospital admission for worsening heart failure and its components, cardiovascular death, and hospital admission for worsening heart failure, was determined in each beta-blocker category using time-to-first event survival analysis-based Cox proportional hazards models containing treatment as a factor and with adjustment for prognostic factors previously used (age, left ventricular ejection fraction, estimated glomerular filtration rate, New York Heart Association functional class, ischemic etiology [yes/no], and systolic blood pressure) (7). Hazard ratios for ivabradine treatment relative to placebo were estimated with 95% confidence intervals and p values calculated from the Wald statistic. Analyses were repeated with and without adjustment for baseline heart rate as a continuous variable. There were no qualitative differences in the models unadjusted for heart rate. Results are reported only for the models adjusted for heart rate. A number of additional models were fitted. First, the differences in treatment effect were analyzed using a general test of heterogeneity across the 5 beta-blocker categories, then with a test for trend in the magnitude of the treatment effect across the beta-blocker categories. In addition, since we have previously demonstrated evidence of a statistically significant interaction between baseline heart rate and the effect of ivabradine (7), we fitted models adjusting also for this interaction. The motivation for this analysis is that the interaction between baseline heart rate and ivabradine treatment suggests that the impact of treatment is greatest in those with the highest baseline heart rate; hence, this might explain why the effect of ivabradine is greatest in those on the lowest dose or no beta-blocker where baseline heart rate is greatest. Finally, to explore the effect of beta-blocker dose on the effects of ivabradine in those taking a beta-blocker, the main analysis was repeated omitting those not taking a beta-blocker.

Results

Baseline characteristics of participants arranged by beta-blocker dose category are given in Table 1. In univariate analysis, not being on a beta-blocker or being on a low dose of beta-blocker was associated with older age, being Asian, and having a lower body mass index, a higher resting heart rate, lower blood pressure, lower ejection fraction, lower rates of taking an angiotensin-converting enzyme (ACE) inhibitor or statin or using devices, and higher rates of taking diuretics or digoxin. Not taking a beta-blocker was particularly associated with a history of chronic obstructive pulmonary disease (COPD), asthma, or peripheral arterial disease and with taking amiodarone. Patients taking calcium channel–blocking drugs were more likely not to be taking a beta-blocker, but if taking a beta-blocker, they were more likely to be on a high beta-blocker dose.

Background beta-blocker dosing. Reasons given by investigators for not administering a beta-blocker or for not reaching the target dose are listed in Table 2. Most frequent reasons for not administering a beta-blocker were COPD, hypotension, asthma, or cardiac decompensation. In those taking a beta-blocker, but not achieving the target dose, the distribution of reasons across the 3 categories were similar to the reasons for beta-blocker nonuse, i.e., hypotension, fatigue, dyspnea, dizziness, cardiac decompensation, and excessive bradycardia.

Independent factors associated with beta-blocker use are given in Table 3. Factors associated with a lower likelihood of taking a beta-blocker are the comorbidities of COPD or asthma, having low blood pressure, having a high heart rate, being older, and taking amiodarone, a calcium channel blocker, or digoxin.

In Table 3, for those taking a beta-blocker, the independent factors associated with a relatively low likelihood of taking at least 50% of the target dose are a history of COPD, a lower blood pressure, a higher heart rate, being older, being treated with amiodarone or digoxin, or not being treated with a calcium channel blocker.

The placebo-corrected effects of ivabradine on heart rate, by categories of baseline beta-blocker doses and baseline heart rate, are illustrated in Figure 1. The analysis of variance model did not provide any evidence of an interaction between beta-blocker dose and baseline heart rate on the placebo-corrected effect of ivabradine on change in heart rate. However, there was evidence of a clear effect of baseline heart rate ($p < 0.0001$), with greatest changes in heart rate at the highest baseline heart rates, but no strong evidence of an additional effect of beta-blocker category ($p = 0.073$). In this model, the effect of the interaction of ivabradine treatment with baseline heart rate remained significant ($p = 0.03$). In analyses of the placebo and ivabradine groups separately, both baseline heart rate and baseline beta-blocker category independently influence ivabradine-mediated change in heart rate.

Effects of ivabradine. The effects of treatment with ivabradine on the primary endpoint or its major secondary endpoints are given in Table 4. Nominally statistically significant reductions in the primary endpoint or hospital admissions for worsening heart failure are demonstrated for those not on beta-blocker and each category of beta-blocker dose <50% of the target dose ($p = 0.012$, $p = 0.007$, and $p = 0.029$; and $p = 0.003$, $p = 0.005$, and $p = 0.009$ for the primary endpoint and hospital admissions for worsening heart failure, respectively). Despite these results and the

Table 1 Baseline Characteristics Split by Baseline Beta-Blocker Category

		Beta-Blocker Dose						
	Overall (n = 6,398)	None (n = 685)	<25% (n = 908)	25%–<50% (n = 1,624)	50%–<100% (n = 1,693)	≥100% (n = 1,488)	p Value Heterogeneity	p Value Trend
Age, yrs	60.3 ± 11.4	64.0 ± 10.9	61.2 ± 11.8	60.5 ± 11.5	59.9 ± 11.1	58.5 ± 11.1	<0.001	<0.001
Male	4,890 (76.4%)	512 (74.7%)	705 (77.6%)	1,254 (77.2%)	1,292 (76.3%)	1,127 (75.7%)	0.594	0.809
Ethnic origin								
White	5,670 (88.6%)	574 (83.8%)	695 (76.5%)	1,423 (87.6%)	1,599 (94.4%)	1379 (92.7%)	<0.001	<0.001
Asian	530 (8.3%)	96 (14.0%)	188 (20.7%)	165 (10.2%)	59 (3.5%)	22 (1.5%)		
Other	198 (3.1%)	15 (2.2%)	25 (2.8%)	36 (2.2%)	35 (2.1%)	87 (5.8%)		
Current smokers	1,106 (17.3%)	131 (19.1%)	157 (17.3%)	285 (17.5%)	304 (18.0%)	229 (15.4%)	0.201	0.068
Body mass index, kg/m^2	28.0 ± 5.1	27.0 ± 5.1	26.4 ± 4.8	27.4 ± 4.8	28.8 ± 4.9	29.2 ± 5.2	<0.001	<0.001
Resting heart rate, beats/min	79.9 ± 9.6	84.2 ± 12.1	80.6 ± 9.9	79.5 ± 9.4	79.1 ± 8.9	78.9 ± 8.6	<0.001	<0.001
Systolic blood pressure, mm Hg	121.5 ± 16.0	121.1 ± 17.3	117.1 ± 16.2	120.0 ± 16.1	122.5 ± 15.4	125.0 ± 14.7	<0.001	<0.001
Diastolic blood pressure, mm Hg	75.6 ± 9.5	74.1 ± 9.9	73.8 ± 9.7	75.0 ± 9.5	76.2 ± 9.2	77.6 ± 9.0	<0.001	<0.001
LVEF, %	29.0 ± 5.2	28.7 ± 5.4	28.1 ± 5.4	28.9 ± 5.2	29.4 ± 4.9	29.3 ± 5.0	<0.001	<0.001
eGFR, ml/min/1.73 m^2	74.6 ± 23.0	71.5 ± 22.8	74.4 ± 26.1	74.2 ± 22.4	74.3 ± 21.5	77.0 ± 22.9	<0.001	<0.001
NYHA functional class								
II	3,110 (48.6%)	287 (41.9%)	419 (46.1%)	821 (50.6%)	849 (50.1%)	734 (49.3%)	<0.001	<0.001
III	3,175 (49.6%)	376 (54.9%)	469 (51.7%)	768 (47.3%)	826 (48.8%)	736 (49.5%)		
IV	111 (1.7%)	22 (3.2%)	20 (2.2%)	33 (2.0%)	18 (1.1%)	18 (1.2%)		
Ischemic heart failure	4,333 (67.2%)	444 (64.8%)	571 (62.9%)	1,120 (69.0%)	1,210 (71.5%)	988 (66.4%)	<0.001	0.024
History of								
MI	3,597 (56.2%)	350 (51.1%)	454 (50.0%)	927 (57.1%)	1,027 (60.7%)	839 (56.4%)	<0.001	<0.001
Hypertension	4,226 (66.1%)	434 (63.4%)	498 (54.8%)	1,029 (63.4%)	1,183 (69.9%)	1,082 (72.7%)	<0.001	<0.001
Diabetes	1,937 (30.3%)	197 (28.8%)	260 (28.6%)	474 (29.2%)	528 (31.2%)	478 (32.1%)	0.207	0.024
Stroke	511 (8.0%)	64 (9.3%)	59 (6.5%)	128 (7.9%)	152 (9.0%)	108 (7.3%)	0.098	0.719
Atrial fibrillation or flutter	510 (8.0%)	61 (8.9%)	70 (7.7%)	132 (8.1%)	140 (8.3%)	107 (7.2%)	0.664	0.301
Dyslipidemia	1,204 (18.8%)	98 (14.3%)	145 (16.0%)	283 (17.4%)	327 (19.3%)	351 (23.6%)	<0.001	<0.001
COPD	721 (11.3%)	224 (32.7%)	95 (10.5%)	174 (10.7%)	152 (9.0%)	76 (5.1%)	<0.001	<0.001
Asthma	174 (2.7%)	74 (10.8%)	15 (1.7%)	29 (1.8%)	32 (1.9%)	24 (1.6%)	<0.001	<0.001
PAD	402 (6.3%)	66 (9.6%)	58 (6.4%)	91 (5.6%)	110 (6.5%)	77 (5.2%)	0.001	0.002
Coronary artery disease	4,636 (72.5%)	476 (69.5%)	605 (66.6%)	1,192 (73.4%)	1,281 (75.7%)	1,082 (72.7%)	<0.001	<0.001
ACE	5,028 (78.6%)	503 (73.4%)	664 (73.1%)	1,276 (78.6%)	1,374 (81.2%)	1,211 (81.4%)	<0.001	<0.001
ARB	913 (14.3%)	129 (18.8%)	129 (14.2%)	213 (13.1%)	214 (12.6%)	228 (15.3%)	0.001	0.103
ACE/ARB	5,826 (91.1%)	620 (90.5%)	785 (86.5%)	1,470 (90.5%)	1,560 (92.1%)	1,391 (93.5%)	<0.001	<0.001
Diuretic	5,325 (83.2%)	589 (86.0%)	786 (86.6%)	1,346 (82.9%)	1,400 (82.7%)	1,204 (80.9%)	0.002	<0.001
Antialdosterone agent	3,883 (60.7%)	399 (58.2%)	591 (65.1%)	1,008 (62.1%)	1,013 (59.8%)	872 (58.6%)	0.009	0.095
Statin	3728 (58.3%)	327 (47.7%)	459 (50.6%)	931 (57.3%)	1,062 (62.7%)	949 (63.8%)	<0.001	<0.001
Calcium-channel blockers	519 (8.1%)	85 (12.4%)	42 (4.6%)	105 (6.5%)	138 (8.2%)	149 (10.0%)	<0.001	0.281
Amiodarone	186 (2.9%)	50 (7.3%)	23 (2.5%)	51 (3.1%)	40 (2.4%)	22 (1.5%)	<0.001	<0.001
Digoxin	1393 (21.8%)	207 (30.2%)	253 (27.9%)	354 (21.8%)	301 (17.8%)	278 (18.7%)	<0.001	<0.001
Devices	243 (3.8%)	23 (3.4%)	28 (3.1%)	52 (3.2%)	65 (3.8%)	75 (5.0%)	0.050	0.010
CRT	72 (1.1%)	9 (1.3%)	11 (1.2%)	20 (1.2%)	12 (0.7%)	20 (1.3%)	0.445	0.716
ICD	206 (3.2%)	15 (2.2%)	23 (2.5%)	46 (2.8%)	56 (3.3%)	66 (4.4%)	0.021	0.001

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstruction pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral artery disease.

apparent trend to reduction in the magnitude of treatment effect with increasing beta-blocker dose, there was no evidence of variation in treatment effect in the general heterogeneity interaction tests (primary composite endpoint p = 0.35) in which adjustment was made for baseline heart rate. In the test formally investigating trends in the treatment effects across beta-blocker category, there were no statistically significant results and a borderline nonsignificant result only for the primary composite endpoint (p = 0.056). After adjusting for the previously identified interac-

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Table 2 Reasons for Not Taking a Beta-Blocker or Not Taking Target Dose

	Beta-Blocker Dose			
	None (n = 685)	<25% (n = 908)	25%–<50% (n = 1,624)	50%–<100% (n = 1,693)
Hypotension	127 (19%)	425 (47%)	717 (44%)	743 (44%)
Fatigue	37 (5%)	289 (32%)	543 (33%)	514 (30%)
Dyspnea	—	135 (15%)	226 (14%)	225 (13%)
Dizziness	21 (3%)	97 (11%)	209 (13%)	206 (12%)
Bradycardia	20 (3%)	48 (5%)	106 (7%)	105 (6%)
Cardiac decompensation	54 (8%)	101 (11%)	144 (9%)	122 (7%)
Other	81 (12%)	67 (7%)	142 (9%)	209 (12%)
COPD	235 (34%)	—	—	—
Asthma	74 (11%)	—	—	—
Raynaud's or PAD	36 (5%)	—	—	—

Values are n (%). Data are presented by categories of the percentage taking target dose. Note: More than 1 reason could be given for not taking target dose of beta-blocker.
Abbreviations as in Table 1.

tion between baseline heart rate and the effect of treatment with ivabradine, the weak evidence of heterogeneity of treatment effect associated with beta-blocker dose was further diluted ($p = 0.14$). In patients with a beta-blocker at baseline, there was no evidence of a trend across the 4 dose categories even in the analysis adjusting only for baseline heart rate ($p = 0.073$ for the primary endpoint, $p = 0.23$ for hospital admission for worsening heart failure, and $p = 0.19$ for cardiovascular death).

Discussion

The present analysis indicates that the effects of ivabradine on the primary clinical outcome of SHIFT, and its components, were not significantly impacted by beta-blocker dose. Any borderline nonsignificant trends were significantly weakened by adjustment for the previously identified interaction between baseline heart rate and ivabradine treatment. This suggests that any impact of background beta-blocker treatment on the effects of ivabradine are, if anything, marginal and that the critical factor driving the benefits of ivabradine treatment is heart rate.

Beta-blockers have well-documented direct effects on cardiovascular and pulmonary function as well as in generating symptoms, e.g., fatigue and dizziness (11,12). Therefore, it is anticipated that differences in background beta-blocker doses would be related to different demographic characteristics in SHIFT participants, such as age or pulmonary comorbidities. In addition, several of these factors have prognostic implications, e.g., age, blood pressure, and left ventricular systolic function (10). The use of devices was low by study design and was addressed in the main SHIFT paper (8). Among the patients included in SHIFT, differences in distribution of comorbidities among groups arranged by background beta-blocker dose are particularly interesting and potentially important in terms of the relation between beta-blocker doses and outcome. For this reason, to minimize outcome differences that might be due to differences in beta-blocker dosing, SHIFT investigators were exhorted to include patients at maximized beta-blocker dose, and the SHIFT protocol prospectively required ascertaining and recording reasons for not using a beta-blocker at all or not reaching guideline-recommended target doses

Table 3 Results of Multivariable Stepwise Logistic Regression

	On a Beta-Blocker vs. Not on a Beta-Blocker	On at Least 50% of the Target Dose
	OR (95% CI), p Value	OR (95% CI), p Value
History of COPD	0.23 (0.19–0.28), <0.0001	0.67 (0.55–0.80), <0.0001
History of asthma	0.13 (0.10–0.19), <0.0001	N/A
DBP, per 5 mm Hg lower	0.90 (0.86–0.95), <0.0001	N/A
SBP, 10 mm Hg lower	N/A	0.82 (0.79–0.85), <0.0001
Heart rate, per 5 beats/min higher	0.81 (0.78–0.84), <0.0001	0.95 (0.92–0.97), 0.0002
Age, per 5 yrs older	0.83 (0.80–0.87), <0.0001	0.91 (0.89–0.94), <0.0001
Treatment		
Amiodarone	0.29 (0.20–0.42), <0.0001	0.63 (0.44–0.89), 0.0093
Calcium-channel blocker	0.52 (0.40–0.69), <0.0001	1.33 (1.07–1.64), 0.0090
Digoxin	0.58 (0.48–0.70), <0.0001	0.75 (0.65–0.85), <0.0001

The multivariable stepwise logistic regression was used to identify independent factors associated with being on a beta-blocker versus not being on a beta-blocker at baseline and to identify independent predictors of being on at least 50% of the target dose among those taking a beta-blocker. Data shown are odds ratios (ORs) and 95% confidence intervals (CIs). An OR <1.00 indicates reduced likelihood of being on a beta-blocker or taking at least 50% of target dose as appropriate. N/A indicates term is not applicable because it was not included in this model.
COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

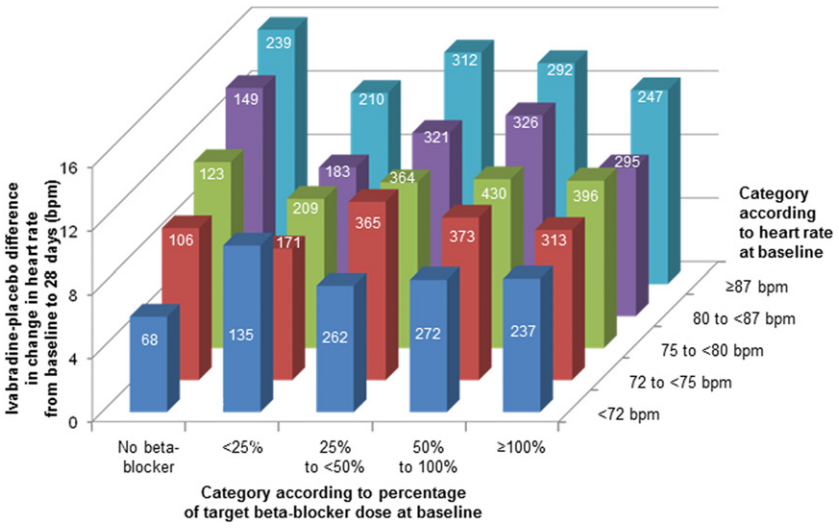

Figure 1 Baseline Heart Rate by Background Dose of Beta-Blockers

Ivabradine–placebo difference in mean change in heart rate from baseline to 28 days in each of the 25 subgroups defined by baseline beta-blocker and heart rate categories.

during beta-blocker up-titration. This information was collected at baseline in a specially designated case report form (9). Thus, intensive effort was made to optimize beta-blocker usage in SHIFT. Despite this effort, only about one-quarter of patients reached recommended target doses, and approximately one-half achieved at least 50% of the target dose. Consequently, it is unclear whether differences in outcome are due to differences in beta blocker doses or differences in the characteristics that limited beta-blocker up-titration.

Nonetheless, the achieved beta-blocker doses in SHIFT are lower than in the landmark beta-blocker studies (13–15)

Table 4 Estimates of the Effects of Randomized Treatment by Category of Baseline Beta-Blocker Treatment Status

				p Value		
	Ivabradine	Placebo	(vs. Placebo) HR (95% CI), p Value	(Interaction) Heterogeneity	(Interaction) Trend*	(Interaction) Trend, Interaction Adjusted†
Primary endpoint						
No beta-blocker	101 (29.4%)	134 (39.3%)	0.71 (0.55–0.93), 0.012	0.35	0.056	0.135
Beta-blocker <25%	148 (30.8%)	171 (40.0%)	0.74 (0.59–0.92), 0.007			
Beta-blocker 25% to <50%	204 (26.2%)	260 (30.8%)	0.81 (0.68–0.98), 0.029			
Beta-blocker 50% to <100%	181 (21.6%)	212 (24.8%)	0.88 (0.72–1.07), 0.193			
Beta-blocker ≥100%	149 (20.1%)	150 (20.1%)	0.99 (0.79–1.24), 0.913			
Hospital admission for worsening heart failure						
No beta-blocker	65 (18.9%)	98 (28.7%)	0.62 (0.45–0.85), 0.003	0.55	0.12	0.19
Beta-blocker <25%	99 (20.6%)	125 (29.3%)	0.68 (0.52–0.89), 0.005			
Beta-blocker 25% to <50%	131 (16.8%)	183 (21.7%)	0.74 (0.59–0.93), 0.009			
Beta-blocker 50% to <100%	124 (14.8%)	154 (18.0%)	0.83 (0.65–1.05), 0.119			
Beta-blocker ≥100%	89 (12.0%)	106 (14.2%)	0.84 (0.63–1.11), 0.223			
CV death						
No beta-blocker	63 (18.3%)	81 (23.8%)	0.80 (0.57–1.12), 0.192	0.68	0.17	0.30
Beta-blocker <25%	84 (17.5%)	96 (22.5%)	0.82 (0.61–1.09), 0.172			
Beta-blocker 25% to <50%	119 (15.3%)	134 (15.9%)	0.95 (0.74–1.22), 0.696			
Beta-blocker 50% to <100%	96 (11.5%)	101 (11.8%)	0.99 (0.75–1.31), 0.930			
Beta-blocker ≥100%	80 (10.8%)	74 (9.9%)	1.08 (0.78–1.48), 0.646			

Values are n (%), unless otherwise indicated. All analyses are adjusted for baseline heart rate, age, left ventricular ejection fraction, estimated glomerular filtration rate, New York Heart Association functional class, ischemic etiology (yes/no), and systolic blood pressure. Three tests are carried out: 1) a general test of heterogeneity; 2) a trend test across the categories of beta-blocker treatment (*); and 3) a trend test adjusted for the interaction between baseline heart rate and treatment (†).

CV = cardiovascular.

of 15 to 20 years ago upon which target dose guidelines are based. However, in those beta-blocker trials, despite a forced titration of the beta-blocker, a considerable number of patients could not reach the target dose at the end of the titration phase (16–18). In addition, a substantial number of patients could not be maintained on the doses achieved after the titration phase and had to reduce or interrupt the treatment due to intolerance during the maintenance phase (18). Moreover, lower doses of beta-blockers in SHIFT might reasonably be expected because treatment patterns and adjunctive therapies have changed in the many years since the landmark beta-blocker trials were performed, for example, with the addition of direct aldosterone antagonism, not regularly employed during the beta-blocker trials.

Thus, it is not surprising that the beta-blocker doses used in SHIFT are thoroughly consistent with doses employed among patients with heart failure in recent international surveys and randomized studies. For example, in the recent CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly) study, Dungen et al. (19) compared the effects of bisoprolol and carvedilol in a randomized trial. Dosing was achieved by forced titration, and target doses were defined, as in SHIFT, according to the ESC guidelines. At least 50% of the target dose was achieved in 55% of the patients, a proportion very similar to that observed in SHIFT. The recent European survey by Maggioni et al. (20) in 3,226 patients with chronic heart failure showed that 87% of patients with heart failure were treated with a beta-blocker, but the target doses of carvedilol, bisoprolol, and metoprolol, as defined by the ESC guidelines, were only reached in 37%, 21%, and 21% of patients, respectively. In another study in primary care in Sweden, pharmacological therapy was optimized to the highest possible dose in relation to ESC recommendations (21). However, beta-blocker use in doses ≥50% was possible in only 62% of patients, and in 57% of patients when the combination of a beta-blocker, an ACE inhibitor, or an angiotensin receptor blocker was considered. In another study in primary care from Scotland, a beta-blocker was used in only 62% and, when used, at least 50% of target doses were reached in 69% and target doses in 34% (22). Based on these experiences, the proportion of patients in contemporary clinical practice (featuring multiple background drugs) who can be titrated to target beta-blocker doses seems to be in the range of 20% to 40%.

For the primary composite outcome in SHIFT, the effect of ivabradine was not significantly associated with the baseline dose of beta-blocker treatment, even in the most statistically powerful trend test, and no association was evident when a general test for interaction was performed. When analysis was adjusted for the previously established interaction between baseline heart rate and ivabradine treatment, any trend that was evident was further weakened. No suggestion of a significant trend was apparent when the analysis was restricted to those taking a beta-blocker. The placebo-corrected treatment effect of ivabradine on heart rate was significantly related to baseline heart rate, but not to beta-blocker dose. Thus, baseline heart rate was the most important contributor to the treatment effect. In the overall trial, the primary driver of the benefit of ivabradine treatment was the effect on hospitalization for heart failure, with no significant benefit on reduction in cardiovascular mortality. Hence, it is worthy of note that there was at least a trend to ivabradine-mediated benefit in reducing heart failure admissions for all categories of beta-blocker treatment, and there was no evidence of heterogeneity of effect across the beta-blocker doses for this outcome.

Moreover, although reduction of heart rate by ivabradine above what is achieved with a beta-blocker and the effect on outcomes by ivabradine have a borderline, nominally nonsignificant relationship to the dose of background beta-blocker therapy, our analysis suggests that this unconfirmed trend may be explained by the confounding impact of the interaction between the effect of ivabradine and baseline heart rate.

The clinical implications of our findings reflect the importance of heart rate as we have previously reported (7). When a resting heart rate >70 beats/min is observed in patients with systolic heart failure in sinus rhythm, the background pharmacological treatment should be reviewed, in particular focusing on the beta-blocker therapy. If an increase of the dose of the beta-blocker can be achieved and results in lowering the heart rate below 70 beats/min, therapy with beta-blocker alone is appropriate. If this goal is not achievable clinically, the addition of ivabradine will result in reduction of the risk of future cardiovascular events.

Study limitations. As a post-hoc subgroup analysis, our findings should be treated cautiously. Our analysis was based on background treatments as optimized by the investigators and not based on a randomized allocation. However, the comparisons between ivabradine and placebo within each beta-blocker category, and the comparisons of treatment effects between beta-blocker categories, are randomized. Inevitably, the numbers of subjects within each beta-blocker category is much smaller than the overall sample size, and hence, power to detect treatment effects and particularly between–beta-blocker category differences in treatment effects is no more than moderate.

Conclusions

Among patients with systolic heart failure, the dose to which a beta-blocker can be titrated is dependent on patient comorbidities and other demographics. By adding the heart rate–lowering agent, ivabradine, in patients whose heart rate exceeds 70 beats/min despite beta-blockade (as well as among those who cannot tolerate beta-blockade), the additional heart rate reduction is beneficial. The magnitude of heart rate reduction by ivabradine beyond what is achieved by a beta-blocker, rather than background beta-blocker dose, primarily determines subsequent outcome.

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Key Words: beta-blockade ■ chronic heart failure ■ heart rate ■ ivabradine ■ treatment.